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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/583,848	GAUGLER ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55,56,63,64 and 66-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55,56,63,64 and 66-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The finality of the previous Office action has been withdrawn, and the prosecution of this application is reopened to include rejections not previously cited.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 54, 57-62 and 65 and adds new claims 68-74, which are related to claim 55 and are not new matter.

Accordingly, claims 55-56, 63-64, 66-74 are being examined.

CONTINUATION DATA

It is noted that the continuation data on the first line of the specification has been updated by the Examiner.

SUBSTITUTE DRAWING

It is noted that the substitute drawing of figure 9 submitted in paper No:12, on 11/27/02 has been approved by the Examiner.

SEQUENCE RULE COMPLIANCE

It is noted that this application still does not comply with sequence rule requirements of 37 C.F.R. 1.821-25, because the sequences recited in the specification still are not accompanied with a sequence identification number, e.g. the sequences recited on page 35 of the specification.

The Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where the sequences without sequence identification numbers may be found.

Appropriate correction is required.

OBJECTION

The oath or declaration is defective because:

It seems that by inadvertent error, application 07/764364, or US 5,327,252 is included in the claimed continuation applications for claiming priority date. US 5,327,252 is related to "Print evaluation apparatus", which is not related to the claimed subjects, and has different inventors than the claimed inventors.

A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP § § 602.01 and 602.02.

REJECTION UNDER 112, FIRST PARAGRAPH, SCOPE

1. Claims 55-56, 63-64, 66-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated cDNA sequence consisting of SEQ ID NO:18, does not reasonably provide enablement for isolated nucleic acid molecule which encodes a fragment of a tumor rejection antigen precursor, or a tumor rejection antigen, wherein the complementary sequence of said isolated nucleic acid molecule hybridizes to the nucleotide sequence set forth in SEQ ID NO:18 at 0.1XSSC, 0.1%SDS for 30 minutes at 65^0C. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 55-56, 63-64, 66-74 are drawn to:

1) An isolated nucleic acid molecule which encodes a fragment of a tumor rejection antigen precursor, wherein the complementary sequence of said isolated nucleic acid molecule hybridizes to the nucleotide sequence set forth in DEQ ID NO:18 at 0.1XSSC, 0.1%SDS for 30 minutes at 65^0C (claim 55), said nucleic acid molecule is cDNA (claim 68), said nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:18 (claim 74).

2) An isolated nucleic acid molecule which encodes a tumor rejection antigen, wherein the complementary sequence of said isolated nucleic acid molecule hybridizes to the nucleotide sequence set forth in SEQ ID NO:18 at 0.1XSSC, 0.1%SDS for 30 minutes at 65^0C (claim 56), said nucleic acid molecule is cDNA (claim 70).

3) An expression comprising the cDNA molecule of claim 68 or claim 70, a host cell transformed or transfected with the nucleic acid molecule of claim 55 or claim 56, wherein the host cell is a mammalian cell or a fibroblast.

The specification discloses that SEQ ID NO:18 or MAGE-6 is a cDNA of 225 nucleotides prepared from mRNAs of a melanoma cell line (Example 32 on pages 35-36). It is noted that the polynucleotide sequence of part of MAGE-6 gene seems to comprise about 4.5 kb, and that MAGEs1-12 polynucleotides that have been sequenced span in the range of 3kb to 4.5kb (De Plaen, E, 1994, Immunogenetics, 40: 360-369,

figure 1 on page 361). Thus it is reasonable to interpret that the polynucleotide of SEQ ID NO:18 or MAGE-6 in the claimed invention is only a cDNA fragment.

The specification further discloses that when various tumor rejection antigens (TRAs) are administered to cells, a CTL response is mounted and presenting cells are deleted, and that this is behavior characteristic of vaccines (p.44, second paragraph). The specification also discloses that a fragment of tumor rejection antigen precursor (TRAP) refers to peptides which are smaller than TRAP, but which possess the properties required for a vaccine (specification, p.44, second paragraph). The specification further discloses that the most noteworthy aspect of the TRAs and TRAPs of the claimed invention is as vaccines for treating" various cancerous conditions" (p.44, lines 16-18), and that vaccines of the type described herein may be used to prevent onset of a "cancerous condition" (p.44 last line bridging p.45).

In addition, the specification discloses that "nucleic acid molecule" refers to all species of DNA and RNA (p.42, lines 13-14).

There are insufficient examples or data showing that the polypeptide encoded by SEQ ID NO:18 of MAGE-6 actually is a target of specific CTLs leading to lysis by CTLs, or can be used for treating or preventing cancers. Further, no definition of "complementary sequence" is found in the specification.

It is noted that in the interview of 27 August 2003, Applicant pointed out that nucleotides 70-96 of the 225 nucleotide sequence of SEQ ID NO:18 of the claimed invention encode a 9 amino acid peptide which is the same as SEQ ID NO:9 of MAGE-6 recited in US 5,405,940 (first page). Applicant further asserted that SEQ ID NO:9 has

been patented in claim 8 in US 5,405,940, and that SEQ ID NO:9 is within a family of nonapeptides having Glu at its N terminal, Tyr at its C-terminal, and Asp at the third residue from its N terminal, wherein said nonapeptides bind to a human leukocyte antigen molecule on a cell to form a complex, said complex provokes lysis of said cell by a cytolytic T cell specific to said complex (claim 1 in US 5,405,940). The Examiner takes note that in US 5,405,940 only SEQ ID NO:1 has been shown to be a target of specific CTLs, leading to lysis by CTLs, and that the data from figure 2 of US 5,405,940 only indicates that the first and ninth amino acids are critical for binding and effecting lysis (column 5, last paragraph and figure 2 of US 5,405,940). The Examiner further takes note that although SEQ ID NO:1 is a target of specific CTLs, leading to lysis by CTLs, SEQ ID NO:9 of MAGE-6 is different from the 9 amino acid peptide of SEQ ID NO:1 of MAGE-1 at amino acids at positions 2, 5 and 8 (see first page of US 5,405,940), and the effect of this difference on the ability to be presented and recognized by specific CTLs is unpredictable, because for presentation of antigen, the antigen has to specifically bind to and fit into a particular groove of the MHC molecule, as taught by Roitt et al, 1998, of record.

In addition, Applicant pointed out that the 9 amino acid peptide encoded by nucleotides 70-96 of the claimed SEQ ID NO:18 is different from the 9 amino acid peptide of SEQ ID NO:17 of MAGE-3 by only one amino acid at position 8 and that SEQ ID NO:17 could be a target of specific CTLs, leading to lysis by specific CTLs (US 6,488,932, claim 1).

Further, in the interview of 27 August 2003, Applicant argues that based on the disclosure in US 5,405,940 and US 6,488,932, it is more likely than not that the 9 amino acid peptide encoded by nucleotides 70-96 of the claimed SEQ ID NO:18 could be a target of specific CTLs, leading to lysis by specific CTLs. Applicant also argues that as disclosed in the specification, the claimed tumor rejection antigen (TRAs) may be used as vaccines and that a fragment of tumor rejection antigen precursor (TRAP) refers to peptides which are smaller than TRAP, but which possess the properties required for a vaccine (specification, p.44, second paragraph).

It is noted that Applicant argues limitation not in the claims. The Examiner takes note that the 9 amino acid peptide of SEQ ID NO:9, which is encoded by the polynucleotide of SEQ ID NO:18 of the claimed invention, is a conservative substitution of the 9 amino acid peptide of SEQ ID NO:17 disclosed in US 6,488,932 because the amino acid at position 8 for SEQ ID NOs: 17 and 9 is Leu (L) and Val (V), respectively, wherein Leu is a conservative substitution of Val. The Examiner further takes note that SEQ ID NO:17 disclosed in US 6,488,932, has been shown to be a target of specific CTLs, leading to lysis by CTLs, and used in a method for treating a patient afflicted with cancer which expresses a tumor rejection antigen precursor and presents HLA-A1 molecules on cell surfaces of said cancer. However, although, being a conservative substitution of SEQ ID NO:17 recited in US 6,488,932, SEQ ID NO:9 encoded by the polynucleotide of SEQ ID NO:18 of the claimed invention is expected to be a target of specific CTLs, leading to lysis by CTLs, the claims as currently constituted, are not

limited to a polynucleotide consisting of SEQ ID NO:18, but encompass unrelated sequences with unknown structure and function (see further details below).

It is further noted that in view of the lack of definition of "the complementary sequence" in the specification, the complementary sequence could be reasonably interpreted as a partial or full length complement, wherein a partial complement could share with the claimed nucleic acid molecule encoding a fragment of a tumor rejection antigen precursor or a tumor rejection antigen only a few nucleotides.

In addition, it is noted that hybridizing under the hybridization conditions at 0.1XSSC, 0.1%SDS for 30 minutes at 65^0C as recited in claims 55 and 56 does not preclude hybridizing to only part of SEQ ID NO:18.

It is also noted that due to the language "comprising" of claim 74, the claim 74 encompasses a nucleic acid molecule of any length, and any structure provided it comprises the 225 nucleotides of SEQ ID NO:18 and has the properties of a fragment of a tumor rejection antigen precursor.

Thus, claims 55-56, 63-64, 66-74 encompass nucleic acid molecules with unknown structure and function, that could be used as a vaccine for treating any cancer, the partial complementary sequences of which are attached to either to the full length or part of SEQ ID NO:18 at 0.1XSSC, 0.1%SDS for 30 minutes at 65^0C. For example, the claims could be reasonably interpreted as encompassing the following sequences that could be used as a vaccine: 1) a polynucleotide sequence that is similar to SEQ ID NO:18, but is larger than SEQ ID NO:18 and hybridizes to the full length of SEQ ID NO:18, the structure of said claimed nucleic acid molecule however is not disclosed in

the specification, nor in the claims, or 2) a polynucleotide sequence comprising a fragment that is similar to a fragment of SEQ ID NO:18 and hybridizes to SEQ ID NO:18 via said shared fragment, the structure of said claimed nucleic acid molecule however is not disclosed in the specification, nor in the claims, or 3) a nucleic acid molecule which has the above sequence of (1) or (2) as a partial complement, wherein the shared complementary portion between the sequences of (3) and (1) or (2) is not necessarily similar to any part of SEQ ID NO:18.

A. One cannot extrapolate the teaching in the specification to the claims 55-56, 63-64, 66-74, because the claims encompass variants of SEQ ID NO:18 or MAGE-6 having any structure, and any length and encoding a peptide or polypeptide of any function or biological activity, which is unrelated to the biological activity of full length MAGE-6. Applicants have not shown how to make and use the claimed variant nucleic acid molecules which are capable of functioning as that which is being disclosed.

It is noted that the biological activity of MAGE proteins is not known (Kirkin, AF et al, 1998, APMIS 106: 665-679, especially page 667, second column, last paragraph).

Further, even if the biological activity of MAGE-6 is known, one cannot predict that the polypeptide sequences encoded by the claimed variants of SEQ ID NO:18 would have any biological activity related to that of MAGE-6, because even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. The following teaching of the art, although drawn to proteins, would apply as well the claimed polynucleotide variants of SEQ ID NO:18, because polynucleotide sequences

encode proteins. It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology, and such unpredictability would equally apply to DNA sequences which encode proteins. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of

the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

The specification does not disclose how to make the claimed nucleic acid molecules comprising SEQ ID NO:18, and the claimed hybridizing nucleic acid molecules, such that they would function as claimed.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

B. Further, claims 55-56, 63-64, 66-73, as drawn to a nucleic acid molecule encoding "a fragment of tumor rejection antigen precursor" or "a tumor rejection antigen", wherein the complementary sequence of which hybridizes to the nucleotide sequence set forth in DEQ ID NO:18 at 0.1XSSC, 0.1%SDS for 30 minutes at 65^0C, are rejected under 112, first paragraph, because one cannot predict that the claimed nucleic acid molecules would have the vaccine properties of "a fragment of tumor rejection antigen precursor" or "a tumor rejection antigen", as defined in the specification, and could be used to treat or prevent cancer.

It is well known in the art that not any peptide from a protein deduced from a polynucleotide is able to bind to HLA, and to stimulate and generate specific CTLs. Roitt I et al, 1998, Immunology, 4th ed, Mosby, London, page 7.9, teach that only a minority of peptide fragments from a protein antigen are able to bind to a particular MHC molecule. Thus, one cannot predict which peptides or whether there is any peptide encoded by the nucleic molecules that hybridize to SEQ ID NO:18 or complements thereof, that could stimulate and generate specific CTLs.

There is insufficient guidance regarding the parameters and sequence of peptides encoded by the claimed nucleic acid molecules, which correlate with the ability to stimulate and generate CTLs. There is insufficient guidance regarding selection of peptides that meet the instant criteria of generating CTLs that kill tumor cells.

Further, even if the claimed nucleic molecules that hybridize to SEQ ID NO:18 encodes some peptides that could be a target of specific CTLs, leading to lysis by specific CTLs, the ability to induce CTL lysis *in vitro* by some MAGE peptides such as those from MAGE-1 and MAGE- 3 does not correlate with vaccine properties, i.e. treating or preventing melanoma cancer. It is well known in the art that MAGE proteins have very low immunogenicity, and that eventhough the MAGE-A3 peptide EVDPIGHLY (same as SEQ ID NO:17 of MAGE-3 in US 6,488932) could cause tumor regression in some metastatic melanoma patients, the CTL response *in vivo* is hardly detectable and requires a specific sensitive detection method (Chaux, P et al, 1998, Intl J Cancer, 77: 538-542, Kirkin, AF et al, 1998, APMIS 106: 665-679). The art teaches that peptides for MAGE-A1 and MAGE-A3 have been tested for their ability to induce

anti-melanoma immune response *in vivo*, and limited anti-tumor activity has been shown only for the MAGE-A3 peptide EVDPIGHLY (same as SEQ ID NO:17 of MAGE-3 in US 6,488932). Thus, although the ability to present CTL epitopes *in vitro* recognized by CTL have been shown for some antigenic epitopes of MAGE-A1, such as EADPTGHSY (same as SEQ ID NO:1 of MAGE-1 in US 5,405940), and SAYGEPRKL, and four epitopes have been identified for MAGE-3, except for the MAGE-A3 peptide EVDPIGHLY, none of other identified peptides have been found to have the ability induce CTLs *in vivo*, or have limited anti-tumor activity (Kirkin, AF et al, 1998, APMIS 106: 665-679, especially page 666, last paragraph of first column, bridging second column, and second paragraph of second column of p.666, and p.669, second paragraph of second column). In other words, the ability to induce CTL lysis *in vitro* by some MAGE peptides such as those from MAGE-1 and MAGE- 3 does not correlate with vaccine properties, i.e. treating or preventing melanoma cancer.

In addition, the specification provides no exemplification of or guidance on how to use the peptide encoded by the claimed polynucleotide for vaccination or for active immunotherapy in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the

later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph). In addition, Boon teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para2).

Moreover, it is well known in the art that anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for

chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed nucleic acid molecule could be used as a vaccine for treating or preventing cancer. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the peptides encoded by the claimed nucleic acid molecule could be used as a vaccine for treating or preventing cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by

serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

Thus based on the teaching in the art, one cannot predict that the claimed nucleic acid sequences would encode peptides having the vaccine ability of treating, or preventing cancer *in vivo*.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

C. Further, even if Applicant could overcome the above 112, first paragraph rejection in item (B), claims 55-56, 63-64, 66-73 and also claim 74 are still rejected under 112, first paragraph, because one cannot predict that the claimed nucleic acid molecules would have the vaccine properties of "a fragment of tumor rejection antigen precursor" or "a tumor rejection antigen", as defined in the specification, and could be used to treat or prevent "any cancer".

It is unpredictable that the claimed nucleic acid sequences comprising SEQ ID NO:18, and the claimed variants whose complementary sequences hybridize to SEQ ID NO:18, would encode peptides having the vaccine properties of preventing or treating "any cancer", because different cancers have different etiology and properties, and respond to a drug differently. Further, not any cancer cell would overexpress or express

on its cell surface the melanoma polypeptide encoded by the claimed nucleic acid sequence comprising SEQ ID NO:18, especially in view of the disclosure in the art that the function of MAGE proteins is unknown, wherein some of the MAGEs such as MAGE-A1 and MAGE-A3 have a cytoplasmic localization, whereas MAGE-A11 has a nuclear localization (Kirkin, AF et al, 1998, *supra*, p.667, last paragraph, second column).

The specification does not disclose how to make the claimed nucleic acid molecules comprising SEQ ID NO:18, and the claimed variants whose complementary sequences hybridize to SEQ ID NO:18, such that they would encode peptides having vaccine properties of treating or preventing any cancer.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

D. In addition, due to the language "a nucleic acid molecule", and in view of the definition of "a nucleic acid molecule" in the specification (p.42, lines 13-14), claims 55-56, 63-64, 66-67, 72-74 encompass a gene sequence.

The specification only discloses a small cDNA fragment of MAGE-6 of SEQ ID NO:18, consisting of 225 nucleotides in length, *supra*.

The specification fails to identify and describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the gene. The art indicates that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically determined (Harris et al. J. of The Am Society of

Nephrology 6:1125-33, 1995; Ahn et al. Nature Genetics 3(4):283-91, 1993; and Cawthon et al. Genomics 9(3):446-60, 1991). Therefore, the structure of these elements is not conventional in the art and one of skilled in the art would not know how to make the claimed invention.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

MINH TAM DAVIS

September 20, 2003